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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Docket No. 06D-0044**
**Draft Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims**

Abbott Laboratories (Abbott) offers the following comments on the draft Guidance for Industry, *Patient-Reported Outcome (PRO) Measures: Use in Medical Product Development to Support Labeling Claims*, published in the *Federal Register* on February 3, 2006.

## General Comments

In general, we find the analysis and interpretation of PROs, as described in this guidance, overly rigorous for general purposes. The Agency's approach appears directed toward the inclusion of a PRO claim in the *Indications* section of labeling. However, many sponsors are using PROs in ongoing and recently completed Phase III clinical trials as secondary measures to report the results from protocol-specified analyses in the *Clinical Studies* section of labeling. Thus, the proposed high standards of data analysis and interpretation laid out in this draft guidance are overly proscriptive. It would be helpful if the Agency revised the guidance to reflect the many uses of PROs.

Section IIIA of this guidance emphasizes the use of PROs in assessing effectiveness, but fails to address the use of PROs to evaluate safety-related measures, such as undesirable adverse effects that can be equally important to patients. Therefore, we suggest that the Agency give equal weight to efficacy and safety-related uses of PROs throughout the guidance.

Although Section IV of this guidance speaks to development of a new PRO instrument, the guidance does not discuss using existing instruments to support a PRO statement in labeling. The guidance should address this important topic.

Lastly, this guidance does not directly address preference-based measures (e.g. Health Utilities Index [HUI], Euroqol-5D [EQ 5D]) that are routinely being collected in clinical trials. These measures provide information on the value that a patient places on current health status. Line 492 cautions against using community-derived preference weights in clinical trials. However, this advice is contrary to published evidence that preference weights from the general community differ little from those provided by patients. In settings where they differ, patients

with disease have higher preference for the same state compared to the general population. It would be helpful if the guidance addressed the subject of preference-based measures.

In addition to the general comments above, we offer these specific comments in order of their appearance in the draft guidance as indicated by section number and line number.

**Specific Comments**

I. INTRODUCTION
Lines 31-32: *A PRO is a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else).*

This definition is too limited as it excludes PROs collected by proxy in special populations that are unable to speak for themselves (e.g. cognitively impaired persons, infants, and young children). We suggest that the definition be modified to read, *A PRO is a measurement of any aspect of a patient's health status that comes directly from the patient (i.e. . . . . .),* ***or when patients are unable to speak for themselves (e.g. cognitively impaired, pediatrics), is provided by immediate caregivers.***

II. BACKGROUND
Lines 85-88: *Rather to substantiate such a general claim, a sponsor should develop evidence to show not only a change in symptoms, but also how that change translates into other specific endpoints such as ability to perform activities of daily living, or improved psychological state.*

This sentence is subjective as written and could be improved if it read, *Rather to substantiate such a general claim, a sponsor should* ***use PRO measures that not only assess*** ~~*develop evidence to show not only*~~ *a change in symptoms, but* ***also the impact on*** ~~*how that change translates into other*~~ *specific endpoints, such as ability to* ***function (e.g.*** *activities of daily living) or* ~~improved~~ *psychological state.*

III. PATIENT-REPORTED OUTCOMES – REGULATORY PERSPECTIVE
Lines 154-156: *PRO instruments that are used in clinical trials to support effectiveness claims should measure adverse consequences of treatment separately from the effectiveness of treatment.*

This sentence should be deleted. There are well-validated tools, such as the FACIT-Fatigue, that measure effectiveness and adverse events together and should be permitted. For example, fatigue could be a symptom of a disease or an adverse reaction due to a treatment.

IV. EVALUATING PRO INSTRUMENTS
Line 178: *When considering an instrument that has been modified from the original, the FDA generally plans to evaluate the modified instrument just as it would a new one.*

This sentence should acknowledge that very modest changes in an instrument do not require revalidation. Therefore, this sentence should read, *When considering an instrument that has been **significantly** modified from the original, the FDA generally plans to evaluate the modified instrument just as it would a new one. **Minor modifications may not require revalidation.*** This same thought appears in Section IVD, where minor changes should not require revalidation and in Line 621 where *wording or placement of instruction* is too minor a change to require revalidation.

Line 275: *The FDA plans to compare the patient population used in the PRO instrument development process to the study populations enrolled in clinical trials to determine whether the instrument is appropriate to that population with respect to patient age, sex, ethnic identity, and cognitive ability.*

The variables listed are too specific and not all inclusive. It would be more accurate to state, *The FDA plans to compare the patient population used in the PRO instrument development process to the study populations enrolled in clinical trials to **ensure that they are similar** ~~determine whether the instrument is appropriate to that population with respect to patient age, sex, ethnic identity, and cognitive ability~~.*

Line 527: *The extent to which the PRO instrument's ability to detect change varies by important patient subgroups (e.g. sex, race, age, or ethnicity) can affect clinical trial results.*

This sentence implies that sponsors are required to validate all PRO tools in important subgroups. We suggest that this sentence should be deleted such that the paragraph consists of the two remaining sentences and encourages sponsors to identify subgroup differences when important.

Line 567: The Agency is specifically asking for comment on the need for, and appropriate standards for, MID definitions applied to PRO instruments used in clinical studies.

We would recommend against the use of MID. MID is not an exact science; different methods may yield different results. Also, when the same methods are utilized in different studies, they may yield different results. Furthermore, MID research may not be applicable as disease treatment patterns change over time. Of the methods described in Lines 550-564, clinical anchor based methods seem the most objective. However, the ideal MID would be the one that would provide convergence of all different techniques. Degrees of concordance between the MIDs using different techniques could be used to verify the convergence of MIDs from different methods[1].

[1] *What is a clinically meaningful change on the Functional Assessment of Cancer Therapy – Lung (FACT-L) Questionnaire?* Results from the Eastern Cooperative Oncology Group (ECOG) Study 5592. Cella et al. *Journal of Clinical Epidemiology* 55(2002) 285-295.

Line 662: The first two bullets of this section should be deleted. Most PROs are not developed specifically for use in clinical trials, although they may prove ultimately useful in the clinical trial setting. The inclusion of a validated PRO in a battery of measures should not entail validation even if the instrument was validated for stand-alone use.

**Editorial Suggestions**

Finally, we offer the following editorial recommendations for the Agency's consideration.

Line 99: *perspective about the effectiveness of a treatment;* ~~**or**~~ *(3) systematic . . .*

Line 123: **well being** ~~**function**~~ *is not new. In clinical practice, to obtain information . . .*

Should you have any questions about this letter, please contact Ms. Lauren Hetrick, Senior Director, Regulatory Intelligence/FDA Liaison Office at (301) 255-0080.

Sincerely,

Lauren M. Hetrick

for Douglas L. Sporn
Divisional Vice President